

Remarks

Claims 52-80 are pending. Claims 49-51 and 55 have been newly cancelled. Claims 52-54 and 56-57 have been newly amended. Claims 58-80 are newly added. Support for these amendments are found throughout the specification and in the claims as originally filed. No new matter has been entered. All newly added claims are encompassed by Group I of the restriction requirement drawn to methods of identifying biomarkers for schizophrenia and methods for diagnosis and prognosis of schizophrenia, further restricted to the CLC gene.

Claims 71, 72, 73, 74 and 77 clarify that said levels of RNA encoded by said gene are in blood samples leukocytes which include all of the types of leukocytes in whole blood, i.e. of blood samples which include granulocytes in addition to mononuclear cells (T-lymphocytes, B-lymphocytes and monocytes). This phrase finds clear support in the specification, including at Figure 5C which shows standardized levels of insulin gene in each of the fractions of leukocytes which collectively constitute unfractionated leukocytes, i.e. granulocytes, T-lymphocytes, B-lymphocytes and monocytes (labeled "G.R.", "CD 3+", "CD19" and "MONO", i.e., respectively). It is well known to the ordinarily skilled artisan that CD3 and CD19 are specific cell surface markers of T-lymphocytes and B-lymphocytes (refer, for example, to the enclosed Abstract of Casey *et al.*, 1988. simplified plastic embedding and immunohistologic technique for immunophenotypic analysis of human hematopoietic and lymphoid tissues. Am J Pathol. 131:183-9). The fact that granulocytes (G.R.), lymphocytes [T-lymphocytes (CD 3+) and B-lymphocytes (CD19+)] and monocytes (MONO) represent all of the types of leukocytes found in blood is taught at Fig. A.23 Immunobiology. Garland Publishing. 2001. Fifth Edition. Janeway, Travers, Walport, and Shlomchik, eds. (attached) which clearly teaches that leukocytes are composed of granulocytes and mononuclear cells, and that the latter are composed of lymphocytes and monocytes. Additional support for the term "leukocytes" is found at paragraphs [0004] and [0089] of the Published Application.

New independent claim 79 claims a method of classifying gene expression in a test subject relative to a population of control subjects that includes subjects having schizophrenia and healthy subjects. New claim 79 comprises a step of quantifying a level of RNA encoded by a

CLC gene in a blood sample from the test subject, and a subsequent step of comparing the level in the sample from the test subject with levels of RNA encoded by the gene in blood samples from the subjects having schizophrenia and in blood samples from the healthy subjects. The new claim concludes that a determination that the level in the sample from the test subject is statistically similar to the levels in the samples from the subjects having schizophrenia and is statistically different from the levels in the samples from the healthy subjects classifies the level in the sample from the test subject with the levels from the samples from the subjects having schizophrenia; and/or concludes that a determination that the level in the sample from the test subject is statistically different from the levels in the samples from the subjects having schizophrenia and is statistically similar to the levels in the samples from the healthy subjects classifies the level in the sample from the test subject with the levels in the samples from the healthy subjects. Support for reciting comparison of biomarker RNA levels of a test subject with those of control subjects having a disease (i.e. schizophrenia) and with those of healthy control subjects, and determination of a statistically significant similarity or difference there between can be found in the published application US **20070105121** (hereinafter “Published Application”), for example at paragraph [0117] (“*when comparing two or more samples for differences, results are reported as statistically significant when there is only a small probability that similar results would have been observed if the tested hypothesis (i.e., the genes are not expressed at different levels) were true*”), at paragraph [0118] (“*when comparing two or more samples for differences, results are reported as statistically significant when there is only a small probability that similar results would have been observed if the tested hypothesis (i.e., the genes are not expressed at different levels) were true*”). Support for reciting classification of a test subject level with specific control levels can be found, for example, at claim 12 as originally filed (“*d) determining whether the level of said one or more gene transcripts of step a) classify with the levels of said transcripts in step b) as compared with the levels of said transcripts in step c)*”), at paragraph [0124] (relating to “*Methods that can be used for class prediction analysis*”), [0351] (“*Blood samples were taken from patients who were diagnosed with schizophrenia as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease.*”).

Specification

The specification is objected to due to new matter submitted in the amendment filed July 29, 2004, incorporating by reference newly added priority document 10/601,518. Accordingly applicant has amended the specification to remove the incorporation by reference of 10/601,518. In light of this amendment to the specification, Applicant respectfully requests withdrawal of the instant objection.

Claims Rejection - 35 U.S.C. 112 2nd

Claims 51-57 are rejected under 35 U.S.C. 112, 2nd paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The office action indicates that the recitation of “unfractionated samples of lysed blood” is indefinite. Although Applicant respectfully traverses, Applicant has canceled claim 51 and dependent claim 55 solely for the purposes of advancing prosecution without prejudice for pursuing the unclaimed subject material in another application, rendering the rejection of claims 51 and 55 moot. Applicant has amended dependant claims 52-54 and 55-57 to be dependent from newly added claim 60, which does not recite the phrase “unfractionated samples of lysed blood”.

Claims Rejection - 35 U.S.C. 112 1st

Claims 51-57 are rejected under 35 U.S.C. 112, 1st paragraph, as failing to comply with the written description requirement on the grounds that the instantly recited phrase “unfractionated samples of lysed blood” is new matter. Although Applicant respectfully traverses, Applicant has canceled claim 51 and dependent claim 55 solely for the purposes of advancing prosecution without prejudice for pursuing the unclaimed subject material in another application, rendering the rejection of claims 51 and 55 moot. Applicant has amended dependant claims 52-54 and 55-57 to be dependent from newly added claim 60, which does not recite the phrase “unfractionated samples of lysed blood”.

Claims 49-57 are rejected under 35 U.S.C. 112, 1st paragraph, as failing to comply with the enablement requirement.

Applicant respectfully traverses. Applicant disagrees with the rejection's assertion that the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art.

The rejected claims include the steps of determining the level of RNA encoded by the gene Charcot-Leyden crystal protein (CLC) in a blood sample obtained from a human test subject and comparing it to the level of control RNA encoded by the CLC gene in blood samples from control subjects, wherein the comparison is indicative of schizophrenia in said human test subject.

Applicant specifically traverses the statement on page 5 of the office action that ~~the~~ "the independent claim, as written, states that a comparison of a human test subject CLC RNA level in a blood sample to a control indicates that schizophrenia is present in the test subject", and the statement on page 6 of the office action that the "claims are extremely broad because they set forth that any or all comparison between a test subject and RNA level from "control subjects" is indicative of disease". Applicant clarifies that the phrase "wherein said comparison of said quantified level of step (a) with said quantified level of said control subjects is indicative of schizophrenia in said human test subject" as formerly recited in newly canceled independent claim 43, is a narrowing limitation, limiting the claim to only those comparisons which are indicative of the test subject having schizophrenia, and excluding those comparisons which do not indicate that the test individual has schizophrenia.

However, in the interest of expediting prosecution, Applicant has added new claims which more clearly reflect the intention of the newly cancelled claims. Specific points raised in the instant enablement rejection will be addressed to the extent they are relevant to the newly added claims.

The rejection asserts that the claims are broad with respect to "control subjects", indicating that "control subjects" could encompass patients with schizophrenia, healthy patients, and patients with some other disease such as depression or rheumatoid arthritis, (page 6 of the office action). The instant claims recite three clearly defined sets of controls: i) patients that

have been diagnosed with schizophrenia, ii) patients that are healthy, and iii) patients that do not have schizophrenia. At least one claim, claim 63, limits the controls to healthy subjects.

The rejection asserts that the claims are very broad in scope because they encompass that any level and direction of difference in gene expression between the tested subjects is indicative of disease, (page 6 of the office action). As described above, Applicant disagrees with this claim interpretation. Accordingly, Applicant has newly added claims which specify a direction and a level of difference in CLC expression required to be detected between the blood samples of the test subject and the healthy controls. For example, claim 75 recites “wherein said test subject is a candidate for having if the level of RNA encoded by said CLC gene in said blood sample of from said human test subject is 2.25 times higher than that of said healthy subjects with a p value = 0.0212”, (emphasis added). Such a statistical probability will not likely be achieved comparing one test subject with only two control subjects, there by addressing the concern raised in the instant rejection over the minimum number of controls necessary for a meaningful comparison, page 7 of the instant office action.

By reciting that the controls are healthy subjects, newly added claim 75 also addresses the issue raised in the instant rejection concerning detecting schizophrenia in a test individual based on a comparison between the test individual and control individuals where the control individuals don't have schizophrenia, but could still have some other disease or condition, as suggested at page 7 of the office action. Applicant contends that the specification's disclosure of many genes in addition to the elected CLC gene which are differentially expressed in schizophrenia patients versus healthy patients, does not detract from the CLC gene's being a biomarker for schizophrenia as suggested on page 8 of the office action. Applicant further respectfully traverses the assertion on page 8 of the office action that “there is no guidance or analysis of data in the specification to suggest that this gene in particular is sufficient to conclude that schizophrenia is present”, on the grounds that the specification discloses that RNA encoded by the CLC gene in a blood sample of from a human test subject is 2.25 times higher than that of healthy subjects with a p value = 0.0212, see Example 27 and Table 3Y in which four patients with schizophrenia and six control individuals were analyzed. The rejection also asserts that the specification does not establish any particular level of expression of CLC (relative level or raw level) is sufficient to detect schizophrenia to the exclusion of other disorders, page 8 of the office action, while acknowledging that CLC was not observed to be differentially expressed in any

other disorders described in the numerous examples in the instant specification, page 9 of the office action. While not necessarily agreeing that the claims necessarily categorically excluded all other disorders, solely for the purpose of expediting prosecution, Applicant has included the limitation in claim 75 that the recited comparison between a test subject and controls indicates that the test individual is a “candidate” for having schizophrenia.

The office action indicates that it would take undue experimentation to practice the invention, specifically “to determine difference thresholds required to determine that a patient has or does not have disease”, pages 10 and 13 of the office action, and that the invention is in an area that is highly unpredictable, page 13 and throughout the office action. Applicant respectfully disagrees. MPEP 2164.03 indicates that “the “predictability or lack thereof” in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art.” Because on the guidance in the specification which shows a statistically significant correlation between the levels of CLC RNA in blood of diseased vs. healthy controls, Applicant contends that one of skill can reasonably predict with statistical significant probability that a patient may be a candidate for having schizophrenia based on the teachings in the specification.

Applicant notes that the office action presents no teaching which is inconsistent with the instant claims and/or their support in the specification, including the working examples. Further, the office action cites the larger study by Tsuang et al. which also indicates that CLC RNA displays a statistically significant increase in expression in blood samples of schizophrenia patients vs. healthy controls, see page 8 of office action and 892 form. Because both the specification and a post-filing date reference have demonstrated a reliable relationship between populations of individuals having schizophrenia and healthy controls, Applicant contends it is well within the normal effort and skill of a person in the art to practice the claimed invention. The office action notes that Fjaerli et al teach that CLC is down regulated in whole blood of infants hospitalized with RSV. However, Applicant contends that this teaching is not applicable to the instant invention that CLC is up regulated in schizophrenia patients.

The Examiner also appears concerned as to

“very unpredictable nature of this technology” and cites Iwamoto et al. as teaching that “expression profiling in psychiatric fields have been notoriously discordant”,

Tsuang *et al.* as cautioning that “results must be interpreted with caution given several limitations including small sample size, Vawter *et al.* as teaching “there is a lack of consistency in the study of genes differentially expressed in schizophrenia which might be related to etiological and genetic heterogeneity of the illness” and Cheung *et al.* as teaching “there is a natural variation in gene expression among different individuals”.

Applicant firstly respectfully indicates that Iwamoto *et al.* cites the results of Tsuang *et al.*, which sets forth relevant experimental results in accordance with those of the specification, yet does not refer to any studies which contradict the relevant teachings of the specification or Tsuang *et al.* Vawter *et al.* similarly does not provide any teachings relating to CLC expression, and hence does not provide any teachings contradicting the relevant teachings of the instant specification. Secondly, with respect to use of blood samples, as relates to the instant claims, Iwamoto *et al.* merely addresses the issue of discordance in experimental results which are due to technical differences in the way experiments are performed between different studies performed by different researchers. Iwamoto *et al.* does not suggest that experimental results obtained from blood samples, including those described in the specification and in Tsuang *et al.* are invalid. Iwamoto *et al.* in fact teach that in contrast to the blood-based instant claims, studies performed using brain tissue are particularly prone to inconsistencies due to additional factors specific to post-mortem brain tissue sampling, such as poor quality RNA and high anatomical/cellular heterogeneity of samples (e.g. Table 1). In the case of Vawter *et al.*, Applicant notes that the cited passages relating to data inconsistencies in fact refer to pre-Vawter *et al.* studies which were performed using samples of pre-frontal cortex and which suffer from the drawbacks of using post-mortem brain samples which, similarly to those described by Iwamoto *et al.*, include high variability in mRNA integrity and anatomical/cellular heterogeneity of samples. Vawter *et al.* at p. 42 in fact teaches that use of blood samples overcomes the inconsistencies particular to use of post-mortem brain tissue samples, and thereby in fact supports Applicant’s position that the instant claims are enabled. Applicant respectfully submits that the ordinarily skilled artisan will know to follow the comprehensive and precise technical guidance provided in the specification (refer, for example, to the Examples section of the specification) so as to avoid the discordance issues raised by Iwamoto *et al.* Applicant additionally points out that Iwamoto *et al.* concludes at the last paragraph with the following statement, strongly supporting Applicant’s

position that the instantly claimed methods should be presumed enabled: *“Despite the fact that multiple confounding factors complicate the findings in gene expression profiling in the clinical samples, it is one of the strongest methodologies to reveal the molecular basis of mental disorders, and its importance cannot be overemphasized.”*

With respect to Tsuang *et al.*, which sets forth experimental results regarding CLC expression in accordance with those of the specification, the Examiner states that this reference cautions that the results set forth in the specification must be interpreted with caution due to various potential limitations. Applicant respectfully submits, however, that the preponderance of the teachings of Tsuang *et al.* are nevertheless clearly in favor of the experimental data disclosed therein being reliable. In particular, Tsuang *et al.* clearly teaches that the results are most likely reliable despite the limitations cited by the Examiner, in accordance with the citation: *“Despite these limitations, this work demonstrates the potential utility of blood-based RNA profiling as a diagnostic tool...”* (concluding paragraph of Tsuang *et al.*). Applicant further submits that the experimental results disclosed in Tsuang *et al.* should enjoy a strong presumption of validity in view of this reference being a high-level and peer-reviewed academic publication. Applicant wishes to point out that the cautionary statements set forth in Tsuang *et al.* which were cited by the Examiner clearly represent a maximally conservative interpretation of the data, in line with the maximally conservative standards, for example, of the U.S. FDA for approval of novel medical applications to humans. The Applicant respectfully indicates that it is improper to incorporate the standards for use by the FDA for purposes of determining patentability (see for example Application of Anthony, 56 C.C.P.A. 1443, 414 F.2d 1383, 162 U.S.P.Q. (BNA) 594 (1969); *“We believe that Congress has recognized this problem and has clearly expressed its intent to give statutory authority and responsibility in this area to Federal agencies different than that given to the Patent Office. This is so because the standards established by statute for the advertisement, use, sale or distribution of drugs are quite different than the requirements under the Patent Act for the issuance of a patent.”*

Applicant indicates that Cheung *et al.* provides data concerning a limited number of genes, many of which do not show significant variability and does not provide any data relating to the variability of CLC expression. Applicant further submits that the results disclosed by Cheung *et al.* clearly cannot be reliably extrapolated to primary blood samples since the

lymphoblastoid cells employed by Cheung *et al.* are significantly modified relative to primary blood cells, due to being cultured cell lines generated by immortalization of primary human cells derived from “CEPH” families, as indicated in Reference no. 10 of Cheung *et al.* (Dausset *et al.*, 1990. Genomics 6:575; enclosed) at p. 575, right column, 1st paragraph. Applicant notes that immortalized cultured cell lines such as the lymphoblastoid cells taught by Cheung *et al.* undergo significant genetic modification such as strong genome-wide demethylation (refer, for example, to enclosed abstract of: Vilain *et al.*, 2003. DNA methylation and chromosome instability in lymphoblastoid cell lines. Cytogenet Cell Genet. 90:93), as a result of extensive *in-vitro* culturing in the absence of immune or apoptotic mechanisms which function to eliminate mutated cells in the body. As such, immortalized CEPH lymphoblastoid cells may represent a particularly unsuitable cell type for modeling gene expression variability in primary blood cells since DNA methylation is a major epigenetic mechanism controlling gene expression (refer, for example, to enclosed Abstract of Fitzpatrick and Wilson (Fitzpatrick DR, Wilson CB., 2003. Methylation and demethylation in the regulation of genes, cells, and responses in the immune system. Clin Immunol. 109:37-45).

To the extent that Iwamoto *et al.*, Tsuang *et al.* and Vawter *et al.* and Cheung *et al.* could still be considered to suggest that larger populations of diseased and control populations may be useful to determine what level of differential expression is indicative of disease amongst the population at large, the Applicant submits that the extension of the experiments as outlined in the specification to additional individuals is merely routine. As is noted in *Re Wands* “*even a considerable amount of experimentation is permissible to practice the claimed methods, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.*” (*Re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, the decision *In re Angstadt*, 190 U.S.P.Q. 218 (C.C.P.A. 1976) clearly states that even in an unpredictable art, and clearly permits the presence of a screening step to identify those embodiments which possess the desired activity is permissible. In fact, in *Angstadt*, the Court specifically dismissed the notion that the specification must provide a level of guidance that would predict the outcome of an experiment “with reasonable certainty before performing the reaction” and that “such a proposition is contrary to the basic policy of the Patent

Act, which is to encourage disclosure of inventions and thereby to promote progress in the useful arts.” The “predictability or lack thereof” in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention.

Applicant wishes to point out that in *In re Wands*, the court stated that “[e]nablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. ‘The key word is ‘undue’ not ‘experimentation’ (citing *In re Angstadt*, 537 F. 2d 498 at 504, 190 U.S.P.Q. 214 at 219 (C.C.P.A. 1976)). The Court also stated that “the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.” (citing *In re Jackson*, 217 U.S.P.Q. 804 at 807 (Bd. App. 1982)).

As such the Applicants believe there is sufficient guidance provided by the specification and that the art is sufficiently predictable such that the amount of experimentation to perform the subject matter within the instant claims is not undue.



In light of the amendments and above remarks, the Applicant contends that the claims are fully enabled, and respectfully requests reconsideration and withdrawal of the instant rejections.

Conclusion

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. No new matter is added. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

Date: October 17, 2007

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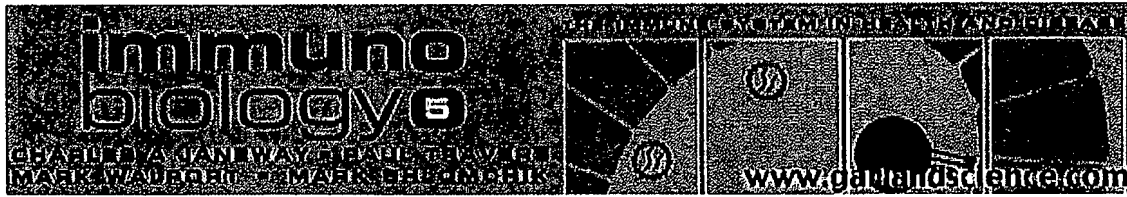
Abstract of Casey *et al.*, 1988. simplified plastic embedding and immunohistologic technique for immunophenotypic analysis of human hematopoietic and lymphoid tissues. Am J Pathol. 131:183-9);

Fig. A.23 Immunobiology. Garland Publishing. 2001. Fifth Edition. Janeway, Travers, Walport, and Shlomchik, eds.

Abstract of Fitzpatrick and Wilson (Fitzpatrick DR, Wilson CB., 2003. Methylation and demethylation in the regulation of genes, cells, and responses in the immune system. Clin Immunol. 109:37-45

Abstract of: Casey et al., 1988. simplified plastic embedding and immunohistologic technique for immunophenotypic analysis of human hematopoietic and lymphoid tissues. Am J Pathol. 131:183-9

Routine fixation and paraffin embedding destroys many hematopoietic and lymphoid differentiation antigens detected by flow cytometry or frozen section immunohistochemistry. On the other hand, morphologic evaluation is difficult in flow cytometric or frozen section studies. A simplified three-step plastic embedding system using acetone-fixed tissues embedded in glycol-methacrylate (GMA) resin has been found to provide both excellent morphologic and antigenic preservation. With our system, a wide variety of antigens are detected in plastic sections without trypsinization or prolonged embedding procedures; **pan-B** (CD19, CD22), **pan-T** (CD7, CD5, CD3, CD2), T-subset (CD4, CD8, CD1, CD25) markers as well as surface immunoglobulin and markers for myeloid and mononuclear-phagocyte cells are preserved. In summary, modifications of plastic embedding techniques used in this study simplify the procedure, apparently achieve excellent antigenic preservation, and facilitate evaluation of morphologic details in relation to immunocytochemical markers.


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Appendix I. Immunologists' Toolbox

Immunization.

The detection, measurement, and characterization of antibodies and their use as research and diagnostic tools.

➔ Isolation of lymphocytes.

Characterization of lymphocyte specificity, frequency, and function.

Detection of immunity *in vivo*.

Manipulation of the immune system.

Immunobiology ➔ Appendix I. Immunologists' Toolbox ➔ Isolation of lymphocytes.

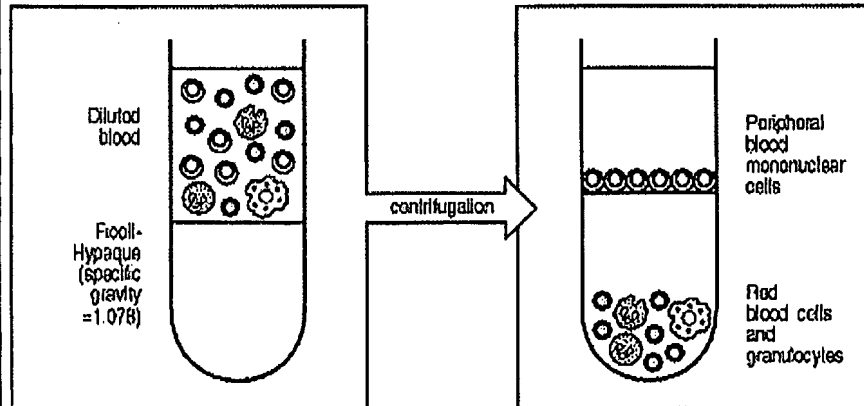


Figure A.23. Peripheral blood mononuclear cells can be isolated from whole blood by Ficoll-Hypaque™ centrifugation. Diluted anticoagulated blood (left panel) is layered over Ficoll-Hypaque™ and centrifuged. Red blood cells and polymorphonuclear leukocytes or granulocytes are more dense and centrifuge through the Ficoll-Hypaque™, while mononuclear cells consisting of lymphocytes together with some monocytes band over it and can be recovered at the interface (right panel).

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FULL-TEXT ARTICLE

Methylation and demethylation in the regulation of genes, cells, and responses in the immune system.

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DNA methylation is a focus of epigenetic research in the immune system. This overview begins with a synopsis of the players and processes involved in DNA methylation, demethylation, methyl-CpG-recognition, histone modification, and chromatin remodeling. The role of these mechanisms in immune responses, with a focus on T lymphocytes, is then reviewed. There is evidence for epigenetic regulation of several key immune processes including thymocyte development, antigen presentation, differentiation, cytokine expression, effector function, and memory. DNA methylation contributes, along with other epigenetic mechanisms, to the establishment of transcriptional thresholds that vary between genes and T cell types. The immune system is a fertile field for studies of epigenetic regulation of cell fate and function.

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